WO 03/103706

PCT/EP03/06095

#### 1/13

# FIG. 1. Rat polypeptide P501S sequence (SEQ ID NO.1)

MIQRLWASRLLRHRKAQLLLVNLLTFGLEVCLAAGITYVPPLLLEVGVEEKFMTMVLGIGPVLGLVSVP
LLGSASDQWRGRYGRRPFIWALSLGVLLSLFLIPRAGWLAGLLCSDTRPLELALLILGVGLLDFCGQV
CFTPLEALLSDLFRDPDHCRQAFSVYAFMISLGGCLGYLLPAIDWDTSALAPYLGTQEECLFGLLTLIF
LICVAATLLVAEEAVLGPPEPAEGLLVSSVSRRCCSCHAGLAFRNLGTLFPRLHQLCCRMPRTLRRLFV
AELCSWMALMTFTLFYTDFVGEGLYQGVPRAEPGTEARRHYDEGIRMGSLGLFLQCAISLFFSLVMDRL
VQKFGTRSVYLASVMTFPVAAAATCLSHSVVVVTASAALTGFTFSALQILPYTLASLYHREKQVFLPKY
RGDAGGGSSEDSQTTSFLLGPKPGAPFPNGHVGPGGSSILVPPPALCGASACDVSMRVVVGEPPEAKVV
TGRGICLDLAILDSAFLLSQVAPSLFMGSIVQLSHSVTAYMVSAAGLGLVAIYFATQVVFDKNDLAKYS
L

# FIG.2. Nucleotide sequence encoding rat P501S (SEQ ID NO.2).

GGGCTCTTAGACACCGCAACAAAAGCAACTTTCCTCCAAGCCACTGCCACCTGTTGGGTTTTCACACAT TTCGAGCTTTAGTTCCGATCCCCAGAACATCCACGTAGTTTTTCTGGCCTTCTGGCTGAGCCATGGAGG CCGACAGAGGAGGGGAGAAGTTTGAAGCTTGAGAAGGATTTCCGTATGCGCAAGGCTACCCATGCTTGT CCTTCCTCCCATGACCCTGGTCAGCCCTCCTCTGCCCTCTTCCTGCCCCCCCTTCTCTCCAGGGTCC GACTGACGAGATGTGTCCCCATCAAGCAAGGCACTAGATGGTGACGTGTTCAGTGTGGGATGAGATGCC GAAGTGGTACTCAAGGGCTGGCCGAAATGGGAGCCTGGCTGCACCCTCGGAGGTTGGTGCTAGCAAGGA GGAGAAGCCGCGGCAGGGCTGACTCAAAACAGCTGTGGGGTGTGTGAATGGCCCCCGGACCCCTAACCG CCCTGTCCATCatgatccagaggctgtgggccagccgtctgctaaggcatcggaaagcccagctcctgc tggtcaacctgctaaccttcggcctggaggtgtgcctggctgctggcattacctatgtgccaccccttc tgctggaagtcggggtagaggaaaagttcatgaccatggtgttgggcattggcccagtgctgggcctgg tttctgttccactcctaggctcagccagtgaccagtggcgtgggcgctatggccgccggagacccttta tactgtgttcagatactaggcccctggagttggccctgctcatcttgggagtggggctgctggactttt geggecaggtgtgctttactccactggaggccttactctccgacctcttccgggacccagaccactgcc gccaagccttctctgtctatgccttcatgatcagcctcgggggctgcctgggctacctcttacctgcca ttgactgggacaccagcgccctggccccctacctaggcactcaggaagaatgcctcttcggcctcctca ccctcatttttctcatctgtgtggcagccactctgcttgtggctgaggaggcagtccttggcccacccg agccagcagaagggttgttggtctcctccgtgtcacgccggtgctgctcatgccatgctggcctggctt teeggaatetgggtaccetgttteeceggetgcaccagetgtgetgeegaatgeetegeaeeetgegee ggctctttgtggctgagctgtgcagctggatggcacttatgactttcacactgttctacacggacttcg aaggcattcgaatgggcagcctggggctcttcctgcagtgtgccatctccctgttcttctccctggtca tggacaggctggtacagaagttcggcacacggtcagtctacctggccagtgtgatgacctttcccgtgg ctgccgctgccacgtgcctgtcccacagcgtggttgtagtgacagcctcagctgccctcaccgggttca

# FIG. 3. Amino acid sequence for Cynomolgus monkey P501S (SEQ ID N°3)

MVQRLWVSRLLRHRKAQLLLINLLTFGLEVCLAAGITYVPPLLLEVGVEEKFMTMVLGIGPVLGLVSVP
LLGSASDHWRGRYGRRRPFIWALSLGILLSLFLIPRAGWLAGLLCPDPRPLELALLILGVGLLDFCGQV
CFTPLEALLSDLFRDPDHCRQAYSVYAFMISLGGCLGYLLPAIDWDTSALAPYLGTQEECLFGLLTLIF
LTCVAATLLVAEEAALGPAEPAEGLSAPSLPSHCCPCWARLAFRNLGALLPRLHQLCCRMPRTLRRLFV
AELCSWMALMTFTLFYTDFVGEGLYQGVPRAELGTEARRHYDEGVRMGSLGLFLQCAISLVFSLVMDRL
VQRFGTRAVYLASVAAFPVAAGATCLSHSVAVVTASAALTGFTFSALQILPYTLASLYHRERQVFLPKY
RGDAGGTSSEDSLMTSFLPGPKPGAPFPNGHVGAGGSGLLPPPPPALCGASACDVSVRVVVGEPTEARVV
PGRGICLDLAILDSAFLLSQVAPSLFMGSIVQLSQSVTAYMVSAAGLGLVAIYFATQVVFDKSDLAKYS
V

# FIG.4. Nucleotide sequence for Cynomolgus monkey P501S (SEQ ID N°3)

PCT/EP03/06095

#### 3/13

ggctgcctgggctacctcctgcctgccattgactgggacaccagtgccctggccccctacctggcacc caggaggagtgcctctttggcctgctcacctcatcttcctcacctgcgtagcagccacactgctggtg tgctgtccgtgctgggcccgcctggctttccggaacctgggcgccctgcttccccggctgcaccagctg tgctgccgcatgccccgcaccctgcgccggctcttcgtggctgagctgtgcagctggatggcactcatg accttcacgctgttttacacggatttcgtgggcgaggggctataccagggcgtgcccagagctgagctg ggcaccgaggcccggagacactatgatgaaggcgttcggatgggcagtctgggggctgttcctgcagtgc gccatctccctggtcttctctctggtcatggaccggctggtgcagcgattcggcactcgagcagtctat ctggccagtgtggcagctttccctgtggctgccggtgccacgtgcctgtcccacagtgtggctgtggtg acggcttcagccgccctcactgggttcaccttctcagccctgcagatcctgccctacacactggcctcc ctctaccaccgggagaggcaggtgttcctgcccaaataccgaggggacgctggaggcactagcagtgag cgtgtggtggtgggtgagcccaccgaggccagggtggttccggggccggggcatctgcctggacctcgcc atcctggatagtgccttcctgctgtcccaggtggccccgtccctgttcatgggctccatcgtccagctc agccagtctgtcactgcctatatggtgtctgctgcaggcctgggtctggttgccatttactttgctaca caggtagtatttgacaagagcgacttggccaaatactcggtgtagAAAACTTCCAGCACATTGGGGTGG AGGGCCTGCCTCACTGGGTCCCAGCTCCCACTCTTTGTTAGCCCCATGGGGCTGCTGGGCTGCCGCC AGTTTCTGTTGCTGCCAAAGTAATGTGGCTCTCTGCTGCCACCCTGTGCTGCTGAGGTGCGTAGCTGCA  ${\tt CAGCTGGGGGCTGGGGCATCCCTCTCCCCCCAGTCTCTAGGGCTGCCTGACTGGAAGCCTTCCA}$ AGGGGGTTTCAGTCTGGACTTCTACAGGGAGGCTAGAAGGGCAGGGCATTTGATTCGCTCCATGCACTG GAATGTGGGGACTCTGCAGGTGGATTACCCAGGCTCAGGGTTAACAGCTAGCCTCCTGGCTGAGACATA CCTAGAGAAGGGGTTTTGGGAGCTGAGTAAACTCAGTCACCTGGTTTCCCACCTCTAAGCCCCCTTAAC  $\tt CTGCAGCTTCATTTAATGTAGCTCTTGCATGGGAGTTTCTAGGATGAAACACTCCTCCGTGGGATTTGA$ ACGTATGAAAGTTATTTGTAGGGGAAGAGTCCTGAGGGGCAACACACCAGGTCCCCTCAGCCCACAGCA CTGCCTTTTTGCTGATCCCCTGACTCTTACCTTTTATCAGGACGTGGCCTATTGGTCCCTTTGTTGCCA CTTTTGTGTGTGTGTGTCTAAGATTTGGGTAGGGTGGGATCCCCAACAATCAGGTCCACTGAGATCACT GGTCATTGGGCTGATCATTGCCAGAATCTTCTTCTCCTGGGGTCTGGCTCCTCAAAATGCCTAACCCAG GACCTTGGAAATTTTACTCATCCCGACTGATAATTCCAAATGCTGTTACCCAAGGTTAGGGGGTTGAAG GAAGGTGGAGGGTGGGGCTTCAGGTCTCAACAGCTTCCCTAACCACCCCTTTTCTCTTGGCCCAGCCTG GTTCCCCCCACTTCTACTCCCCTCTACTGTCTCTAGGACTGGGCTGATGAAGGCACTGCCTGAAATTTC CCTCACCCCAACTTTCCCCACTGGCTCCACAACCCTGTTTGGAGCTGTTGCAGGACCAGAAGCACAAA GTGTGGTTTCCCAGGCCTTTGTCCATCTCAGCCCCCCAGAGTATATCTGTGCTTGGGGAATCTCACACA GAAACTCAGGAGCACCCCTGCCTGAGCTAAGGAGGTCTTATCTCTCAGGGGGGGTTTAAGTGCCGTTTG CAATAATGTCTTATTTATTTAGCGGGGCAAATATTTTATACTGTAAGTGAGCAATCAGTATAATGTTTA 

## FIG.5. Amino acid sequence for human P501S (SEQ ID N°5)

MVQRLWVSRLLRHRKAQLLLVNLLTFGLEVCLAAGITYVPPLLLEVGVEEKFMTMVLGIGPVLGLVCVP
LLGSASDHWRGRYGRRRPFIWALSLGILLSLFLIPRAGWLAGLLCPDPRPLELALLILGVGLLDFCGQV
CFTPLEALLSDLFRDPDHCRQAYSVYAFMISLGGCLGYLLPAIDWDTSALAPYLGTQEECLFGLLTLIF
LTCVAATLLVAEEAALGPTEPAEGLSAPSLSPHCCPCRARLAFRNLGALLPRLHQLCCRMPRTLRRLFV
AELCSWMALMTFTLFYTDFVGEGLYQGVPRAEPGTEARRHYDEGVRMGSLGLFLQCAISLVFSLVMDRL
VQRFGTRAVYLASVAAFPVAAGATCLSHSVAVVTASAALTGFTFSALQILPYTLASLYHREKQVFLPKY
RGDTGGASSEDSLMTSFLPGPKPGAPFPNGHVGAGGSGLLPPPPPALCGASACDVSVRVVVGEPTEARVV
PGRGICLDLAILDSAFLLSQVAPSLFMGSIVQLSQSVTAYMVSAAGLGLVAIYFATQVVFDKSDLAKYS
A

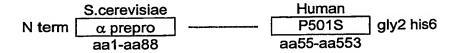
# FIG.6. Amino acid sequence for human P501S (SEQ ID N°6)

GLYQGVPRAEPGTEARRHYDEGVRMGSLGLFLQCAISLVFSLVMDRLVQRFGTRAVYLASVAAFPVAAG ATCLSHSVAVVTASAALTGFTFSALQILPYTLASLYHREKQVFLPKYRGDTGGASSEDSLMTSFLPGPK PGAPFPNGHVGAGGSGLLPPPPALCGASACDVSVRVVVGEPTEARVVPGRGICLDLAILDSAFLLSQVA PSLFMGSIVQLSQSVTAYMVSAAGLGLVAIYFATQVVFDKSDLAKYSA

# FIG.7. Amino acid sequence for human P501S (SEQ ID N°7)

MGSLGLFLQCAISLVFSLVMDRLVQRFGTRAVYLASVAAFPVAAGATCLSHSVAVVTASAALTGFTFSA
LQILPYTLASLYHREKQVFLPKYRGDTGGASSEDSLMTSFLPGPKPGAPFPNGHVGAGGSGLLPPPPAL
CGASACDVSVRVVVGEPTEARVVPGRGICLDLAILDSAFLLSQVAPSLFMGSIVQLSQSVTAYMVSAAA
LGLVAIYFATQVVFDKSDLAKYSA

# FIG. 8: Design of the yeast P501S recombinant protein



# FIG. 9. Amino acid sequence (SEQ ID NO:9) and nucleotide sequences (SEQ ID NO:8) of alpha prepro P501S his

## Nucleotide sequence (SEQ ID NO:8)

ATGAGTTTCC TCAATTTTAC TGCAGTTTTA TTCGCAGCAT CCTCCGCATT AGCTGCTCCA GTCAACACTA CAACAGAAGA TGAAACGGCA CAAATTCCGG CTGAAGCTGT CATCGGTTAC TCAGATTTAG AAGGGGATTT CGATGTTGCT GTTTTGCCAT TTTCCAACAG CACAAATAAC GGGTTATTGT TTATAAATAC TACTATTGCC AGCATTGCTG CTAAAGAAGA AGGGGTATCT CTCGAGAAAA GAGAGGCTGA AGCCatgGTG CTGGGCATTG GTCCAGTGCT GGGCCTGGTC TGTGTCCCGC TCCTAGGCTC AGCCAGTGAC CACTGGCGTG GACGCTATGG CCGCCGCCGG CCCTTCATCT GGGCACTGTC CTTGGGCATC CTGCTGAGCC TCTTTCTCAT CCCAAGGGCC GGCTGGCTAG CAGGGCTGCT GTGCCCGGAT CCCAGGCCCC TGGAGCTGGC ACTGCTCATC CTGGGCGTGG GGCTGCTGGA CTTCTGTGGC CAGGTGTGCT TCACTCCACT GGAGGCCCTG CTCTCTGACC TCTTCCGGGA CCCGGACCAC TGTCGCCAGG CCTACTCTGT CTATGCCTTC ATGATCAGTC TTGGGGGCTG CCTGGGCTAC CTCCTGCCTG CCATTGACTG GGACACCAGT GCCCTGGCCC CCTACCTGGG CACCCAGGAG GAGTGCCTCT TTGGCCTGCT CACCCTCATC TTCCTCACCT GCGTAGCAGC CACACTGCTG GTGGCTGAGG AGGCAGCGCT GGGCCCCACC GAGCCAGCAG AAGGGCTGTC GGCCCCCTCC TTGTCGCCCC ACTGCTGTCC ATGCCGGGCC CGCTTGGCTT TCCGGAACCT GGGCGCCCTG CTTCCCCGGC TGCACCAGCT GTGCTGCCGC ATGCCCCGCA CCCTGCGCCG GCTCTTCGTG GCTGAGCTGT GCAGCTGGAT GGCACTCATG ACCTTCACGC TGTTTTACAC GGATTTCGTG GGCGAGGGGC TGTACCAGGG CGTGCCCAGA GCTGAGCCGG GCACCGAGGC CCGGAGACAC TATGATGAAG GCGTTCGGAT GGGCAGCCTG GGGCTGTTCC TGCAGTGCGC CATCTCCCTG GTCTTCTCTC TGGTCATGGA CCGGCTGGTG CAGCGATTCG GCACTCGAGC AGTCTATTTG GCCAGTGTGG CAGCTTTCCC TGTGGCTGCC GGTGCCACAT GCCTGTCCCA CAGTGTGGCC GTGGTGACAG CTTCAGCCGC CCTCACCGGG TTCACCTTCT CAGCCCTGCA GATCCTGCCC TACACACTGG CCTCCCTCTA CCACCGGGAG AAGCAGGTGT TCCTGCCCAA ATACCGAGGG GACACTGGAG GTGCTAGCAG TGAGGACAGC CTGATGACCA GCTTCCTGCC AGGCCCTAAG CCTGGAGCTC CCTTCCCTAA TGGACACGTG GGTGCTGGAG GCAGTGGCCT GCTCCCACCT CCACCCGCGC TCTGCGGGGC CTCTGCCTGT GALGTCTCCG TACGTGTGGT GGTGGGTGAG CCCACCGAGG CCAGGGTGGT TCCGGGCCGG GGCATCTGCC TGGACCTCGC CATCCTGGAT AGTGCCTTCC TGCTGTCCCA GGTGGCCCCA TCCCTGTTTA TGGGCTCCAT TGTCCAGCTC AGCCAGTCTG TCACTGCCTA TATGGTGTCT GCCGCAGGCC TGGGTCTGGT CGCCATTTAC TTTGCTACAC AGGTAGTATT TGACAAGAGC GACTTGGCCA AATACTCAGC Gggtggacac catcaccatc accattaa

#### Amino acid sequence (SEQ ID NO:9)

MSFLNFTAVL	FAASSALAAP	VNTTTEDETA	QIPAEAVIGY	SDLEGDFDVA	VLPFSNSTNN
GLLFINTTIA	SIAAKEEGVS	LEKREAEAMV	LGIGPVLGLV	CVPLLGSASD	HWRGRYGRRR
PFIWALSLGI	LLSLFLIPRA	GWLAGLLCPD	PRPLELALLI	LGVGLLDFCG	QVCFTPLEAL
LSDLFRDPDH	CROAYSVYAF	MISLGGCLGY	LLPAIDWDTS	ALAPYLGTQE	ECLFGLLTLI

...

VAEEAALGPT	EPAEGLSAPS	LSPHCCPCRA	RLAFRNLGAL	LPRLHQLCCR
AELCSWMALM	TFTLFYTDFV	GEGLYQGVPR	AEPGTEARRH	YDEGVRMGSL
VFSLVMDRLV	QRFGTRAVYL	ASVAAFPVAA	GATCLSHSVA	VVTASAALTG
YTLASLYHRE	KQVFLPKYRG	DTGGASSEDS	LMTSFLPGPK	PGAPFPNGHV
PPALCGASAC	DVSVRVVVGE	PTEARVVPGR	GICLDLAILD	SAFLLSQVAP
SQSVTAYMVS	AAGLGLVAIY	FATQVVFDKS	DLAKYSAGGH	нннн
	AELCSWMALM VFSLVMDRLV YTLASLYHRE	AELCSWMALM TFTLFYTDFV VFSLVMDRLV QRFGTRAVYL YTLASLYHRE KQVFLPKYRG PPALCGASAC DVSVRVVVGE	AELCSWMALM TFTLFYTDFV GEGLYQGVPR VFSLVMDRLV QRFGTRAVYL ASVAAFPVAA YTLASLYHRE KQVFLPKYRG DTGGASSEDS PPALCGASAC DVSVRVVVGE PTEARVVPGR	AELCSWMALM TFTLFYTDFV GEGLYQGVPR AEPGTEARRH VFSLVMDRLV QRFGTRAVYL ASVAAFPVAA GATCLSHSVA YTLASLYHRE KQVFLPKYRG DTGGASSEDS LMTSFLPGPK PPALCGASAC DVSVRVVVGE PTEARVVPGR GICLDLAILD

## FIG.10.

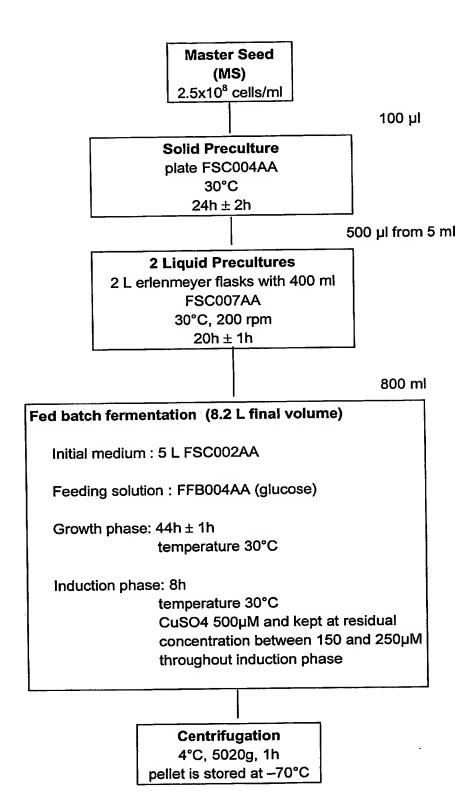
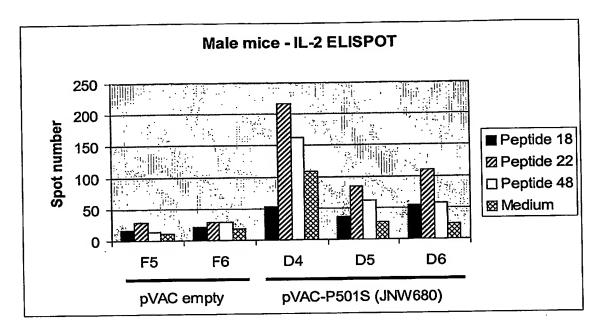


FIG.11.



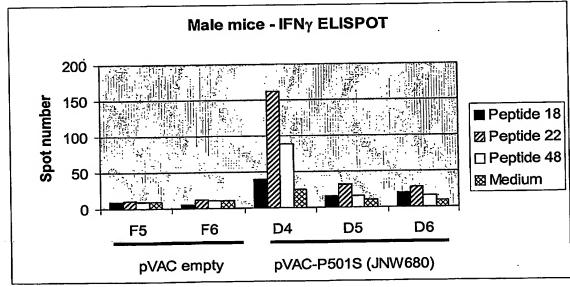
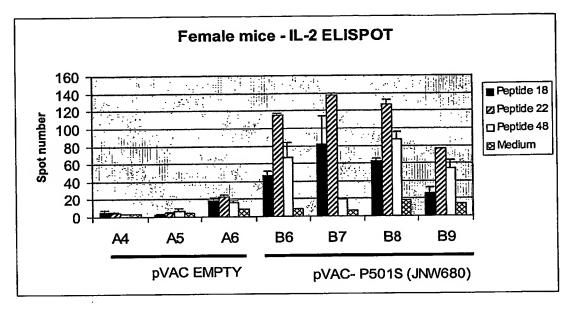
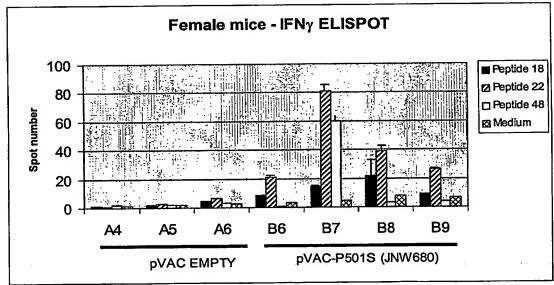


FIG.12.





## FIG.13.

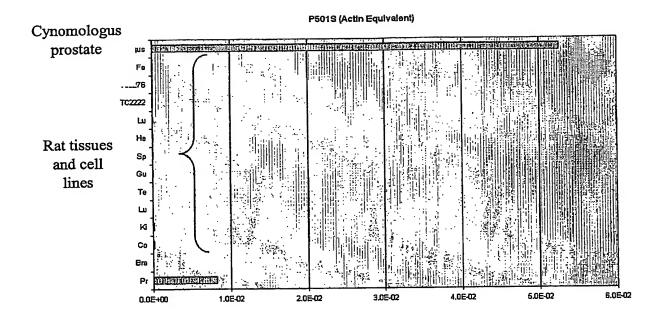


FIG. 14. Amino acid sequence for mouse P501S (SEQ ID N°10)

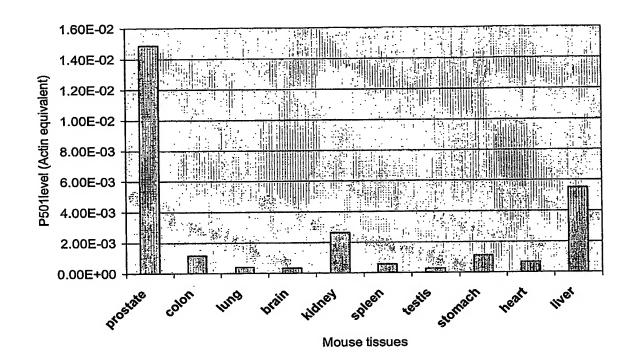
MIQRLWASRLLRHRKAQLLLVNLLTFGLEVCLAAGITYVPPLLLEVGVEEKFMTMVLGIGPVLGLVSVPLGSASDQWRGRYGRRPFIWALSLGVLLSLFLIPRAGWLAGLLYPDTRPLELALLILGVGLLDFCGQVCFTPLEALLSDLFRDPDHCRQAFSVYAFMISLGGCLGYLLPAIDWDTSVLAPYLGTQEECLFGLLTLIFLICMAATLFVTEEAVLGPPEPAEGLLVSAVSRRCCPCHVGLAFRNLGTLFPRLQQLCCRMPRTLRRLFVAELCSWMALMTFTLFYTDFVGEGLYQGVPRAEPGTEARRHYDEGIRMGSLGLFLQCAISLVFSLVMDRLVQKFGTRSVYLASVMTFPVAAAATCLSHSVVVVTASAALTGFTFSALQILPYTLASLYHREKQVFLPKYRGDAGGSSGEDSQTTSFLPGPKPGALFPNGHVGSGSSGILAPPPALCGASACDVSMRVVVGEPPEARVVTGRGCICLDLAILDSAFLLSQVAPSLFMGSIVQLSHSVTAYMVSAAGLGLVAIYFATQVVFDKNDLAKYS

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# FIG.15. DNA sequence for mouse P501S (SEQ ID N°11)

GAGATTTAAAAGGCGCCCGCTGGCGCGCGTTGGTGAMSCAGGBGTCGCCGAGCTCGCACGCCCCAGCCC TGGTGACGTGTTTAGCGTGGGACGAGATGCTGAATTGGCACTAAAGGGCTGGCAGAAATGGGAACCTGG CTGCACCCTAGGAGGTTAGTGCTAGTGAGGAGGAGAAGCCACGGCAGGGCTGACTCAAAGCAGCTGTGG AGTATGTGAGTAGCCCTGGAACCCTACCTGCCCTGTCCATCatgatccagaggctgtggggccagccgt ctgctacggcaccggaaagctcagctcctgctggtcaacctgctcacctttggcctggaggtgtgcctg gctgccggcattacctatgtgccaccccttctgctggaagtcggggtggaggagaaattcatgaccatg gtgttgggcattggcccagtgctaggcctggtttctgttccactcctaggctcagccagtgaccagtgg  $\verb|cgtgggcgctatggccgcggagaccctttatctgggctttgtccctgggtgtcctgctaagcctcttt|\\$ ctcatcccgagggctggctggctggcaggactgctgtacccagacaccaggcccctggagttggccctg ctgatcttgggagtggggctgctggacttttgtggccaggtgtgctttactccattggaggccttactc tccgacctcttccgggacccagaccactgccgccaagccttctctgtctacgccttcatgatcagcctt gggggctgcctgggctacctcttacctgccattgactgggacaccagcgttctggccccctacctgggt actcaggaagaatgcctctttggcctcctcaccctcattttcctcatctgcatggcagccactctgttt gtgacggaggaggcagtactgggcccacccgagccggcagaagggttgttggtctctgccgtgtcgcgc cgatgctgcccatgccacgttggcctggctttccggaatctgggtaccctgtttccccggctgcagcag ctgtgctgccgcatgcctcgcaccctacgccgactctttgtggctgagctgtgcagctggatggcactt atgactttcacactgttctacacggacttcgtgggagaggggctgtaccagggtgtacccagagccgag ccaggcaccgaggcccggagacactatgatgaaggcattcgaatgggcagcctggggctcttcctgcag tgtgccatctccctggtcttctccctggtcatggacaggctggtacagaagttcggcacacggtcagtc gtgacagcctcagctgccctcaccgggttcaccttctcggccttgcagatcctgccttacacgctcgcc  $\verb|tccctctaccaccgtgagaagcaggtgttcctgcccaaataccgaggggacgctggaggtagcagcggt|$ gaggacagccagacaaccagcttcttgccaggccctaagccaggagctctcttccccaatggacacgtg atgcgagtggtggtgggtgagccacctgaggccagggttgttacgggacggggcatttgcctggacctg gccattctggacagtgcctttctgctgtcccaggtggctccgtccctgttcatgggctccattgtccag  $\verb|ctgagccactctgtcactgcctatatggtatcagctgcaggcttgggtctggtcgccatttactttgct|$ acacaggtagtgtttgacaagaacgacttggccaaatactcagtgtagAATTGTGTAAGGCATCAAAGA  ${\tt GAGGGTCTGCCTCATGGGTTCTCAGCCCTTAGAGGGCTGCAGAGCTGGCCTCTCCAGGTCTTTGTCGCC}$ TAAGTGGCTCTCTGCCGCCCCTAAGGCAGTGAGGTGTATTGTTGCACAGATAGGAGCCAGAGCTTTC GGGGCTCTGGCTTCAGAGTCTGGCTGGCCTACTGGCAGCCTCTCGCATG

# FIG.16.



# FIG.17.



